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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/022,127	PANCHAL ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27 and 29-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27, and 29-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

2. The rejection of claims 10-12, 23-26, 33-36 under 35 USC 112, 2nd paragraph is withdrawn in response to Applicant's arguments.

3. Applicant's arguments filed 12-19-03 with respect to the rejection of claims 1-6, 8-11, 13-15, 16-18 and 20-22, and 24-25, and 38-39 under 35 U.S.C. 103(a), have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 32 and 37 remain rejected, and claims 13 and 33-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons of record set forth in the Office Action mailed 11-21-03.

Applicant's arguments filed 12-19-03 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the specification as filed catalogues and thoroughly describes gene delivery systems known in the prior art, and furthermore "for the purposes of enablement, the gene delivery system need not be absolutely

efficient., as optimality is not required for a valid patent". Contrary to Applicant's assertions, although vectors may be available in the art that are able to deliver a gene to a particular tissue, the question remains regarding the production of the desired secondary effect in that particular tissue as a result of the expression of the gene of interest, and furthermore would that expression be sustained long enough in order to treat a disease efficiently? In response to the Examiner's comments regarding the possible toxicological effects of the treatment on the translation of other known and unknown proteins, Applicants state that "this concern may not be important..the rescued protein is expressed at a low level and may show some functional correction, the relatively low efficiency of the tRNA suppressor may not be high enough to result in any significant functional damage to a normal protein, even if some readthrough occurred in normal genes." Applicants have demonstrated the successful suppression of a nonsense mutation in the XPAC gene *in vitro*, however toxicity was observed in this example and Applicants state that it was "likely related to HSV host shut off genes". In response to Applicant's arguments, the issue of possible toxic effects as a result of potential suppressor tRNA interaction with non-target genes still remains, as recognized by Applicants. However, contrary to Applicant's opinion that "this concern may not be important", the behavior of suppressor tRNAs are unpredictable and the nonspecific interaction of a suppressor tRNA with the translation of an essential gene could be potentially devastating to a cell. Furthermore, Applicant's admit that "the relatively low efficiency of the tRNA suppressor may not be high enough to result in any significant damage to a normal protein", this statement leads one to question the relative efficiency of the suppressor tRNA to rescue the translation of nonsense mutations in target genes. In addition, Applicant's also admit that toxicity was observed *in vitro*, this observation was "likely related to HSV host

shut off genes", however it is not clear that this cytoxicity was not due to the readthrough of host genes by the suppressor tRNA. This final observation further complicates the application of this technique *in vivo,* since the behavior of the suppressor tRNA *in vitro* is unpredictable and cytotoxic effects were observed *in vitro*.

As stated previously, the amount of experimentation necessary to determine the appropriate mode of delivery of the suppressor tRNA gene sequence into an animal, to access the possible toxicological effects the treatment may have on the translation of other known and unknown proteins in each cell in said animal is beyond the scope of one with ordinary skill in the art. The instant application contains no guidance in performing all of these experiments, which adds to the difficulty in practicing the invention. The examples presented in the specification do not adequately describe how to use the present invention embodied by claims 13 ad 32-37. When the Wands factors are weighed, it is concluded that undue experimentation would be required to practice the invention throughout the full scope of the claims, and therefore the invention is not enabled.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-6, 8-11, 13-15, 16-22, and 24-25, and 38-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sharp et al., Temple et al., Li et al., Noren et al. in view of Capone and Atkinson et al.

Sharp et al. disclose a method of designing tRNAs which suppress nonsense codons in a gene in a mammalian cell, said method comprising 1) preparing an oligonucleotide primer comprising a region complementary to the nonsense codon; 2) preparing a DNA template for production of a tRNA molecule; 3) forming a suppressor gene from said template and primer by site specific mutagenesis; and 4) transforming the suppressor gene into a mammalian cell, whereby the nonsense codon will be suppressed. This method also includes preparing a template for the insertion of an amino acid chosen from the group consisting of: tyrosine, serine, lysine, tryptophan, leucine, glutamine, glutamic acid, and glycine. Included within the embodiments of this invention are SV40 plasmid vectors containing the suppressor tRNA genes (US Patent No. 4,687, 737; column 2). In addition, Sharp et al. teach a method of monitoring the transduction of cells comprising introducing a suppressor tRNA into cells containing a nonsense mutation in a reporter gene, and observing the expression of the reporter gene as a result of the suppressor tRNA restoring translation of the reporter gene product (col. 7-8).

Temple et al. disclose a functional human suppressor lysine tRNA (containing an anticodon which recognizes the amber termination codon UAG) gene whose length is approximately 76 base pairs, this gene was subcloned into M13mp7 phage. This suppressor lysine tRNA was able to suppress the amber nonsense mutation in β-thalassaemia (p. 338). Li et al. teach the use of a human suppressor serine tRNA which has functions in the rescue of mdx (gene associated with Muscular Dystrophy in humans) gene expression lost due to an Ochre (UAA) mutation.

Noren et al. teach a method of site specific incorporation of un-natural amino acids into proteins, wherein said method comprises replacement of a codon encoding an amino acid of

interest, replacing the codon with a nonsense codon (TAG) by oligonucleotide directed mutagenesis, and designing a suppressor tRNA chemically aminoacylated in vitro to recognize the nonsense codon and direct the amino acid into the protein at the target site (p. 182-183). Both natural and un-natural amino acids can be incorporated into a protein by this method.

None of the above references disclose wherein the human tRNA structural gene coprises no more than twenty 3' flanking residues and no 5' flanking sequences, or wherein the human tRNA structural gene has a total length of less than 150 nucleotides.

Atkinson et al. teach that since the promoters for eukaryotic tRNA genes lie within the structural sequences encoding the tRNA molecule itself, the length of the active transcriptional unit of a tRNA gene may be considerably less than 500 base pairs so that accommodation into a delivery vector may be facilitated (page 1327). In addition, based upon an analysis of codons altered by nonsense mutations, Atkinson et al. suggest that UAG suppressor tRNAs should be designed charged with Trp, Gln and Glu, UAA suppressor tRNAs should be designed charged with Gln and Glu and UGA suppressor tRNAs should be designed charged with Arg (page 1332).

Capone (1995) teach that the removal of the 5' and 3' flanking sequences of a human serine tRNA gene comprising an amber mutation, see Figure 1 and Table 1. Capone teaches that complete removal the 5' flanking sequence does not prevent the modified serine tRNA from functioning as a suppressor tRNA. Additionally, it is noted that serine tRNA mutants comprising only 22 bp of 3' flanking sequence still maintained suppressor activity that was about 30% less than wild-type (see page 467 4th paragraph). Moreover, Capone states that the disclosed results suggest that sequences downstream from the terminator site have little influence on levels of

functional expression of serine tRNA. It is also noted that Capone states that the human tRNA structural gene is only 82 nucleotides in length, see Figure 1.

Although these references do not teach two oligonucleotides in tandem both encoding suppressor tRNA genes, these references do teach oligonucleotides that encode suppressor tRNA genes, the added limitation in claim 4 is an obvious modification of claim 1. In view of the general method of designing and using suppressor tRNAs to by-pass nonsense mutations in proteins in mammalian cells as taught by Sharp et al., the ability of human suppressor tRNAs to suppress nonsense mutations in genes associated with diseases in humans as taught by Tempel et al. and Li et al., the study of codons altered by nonsense mutations and the knowledge given relating to the structure of the tRNA molecule regarding the positioning of regulatory elements taught by Capone and Atkinson et al., it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the instant application to design oligonucleotides encoding human suppressor tRNAs of less than 150 bp and to design methods of use of said human suppressor tRNAs embraced by the claimed invention. One of skill in the art at the time of the instant invention would have been motivated to combine the cited references in the design of the claimed invention because all of the references cited teach various aspects in regards to the preparation and design of suppressor tRNA molecules. One of ordinary skill in the art at the time of the invention would have been motivated to modify the teaching of Sharp et al., Temple et al., Li et al., and Noren et al. with Capone and Atkinson et al. by reducing the size of their disclosed suppressor tRNAs particularly by reducing the size of the 5' and 3' flanking sequences because it is well known in the art that smaller plasmids easier to handle and have a higher transfection efficiency than larger molecules.

Additionally, Applicant's oligonucleotides which encode a synthetic suppressor tRNA and those disclosed in the above references have similar properties, and it is deemed that since such is the case, other claimed limitations not disclosed are deemed obvious. Sufficient evidence of similarity is present to shift the burden to Applicant to provide evidence that the claimed products are unobviously different than the suppressor tRNA molecules disclosed in the references described above.

8. Claims 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sharp et al., Temple et al., Li et al., Noren et al. in view of Capone and Atkinson et al. as applied above and further in view of Okasinski.

Sharp et al., Temple et al., Li et al., Noren et al. and Atkinson et al. teach a general method of designing and using suppressor tRNAs to by-pass nonsense mutations in proteins in mammalian cells (Sharp et al.), the ability of human suppressor tRNAs to suppress nonsense mutations in genes associated with diseases in humans (Tempel et al. and Li et al.), and the study of codons altered by nonsense mutations and the knowledge given relating to the structure of the tRNA molecule regarding the positioning of regulatory elements (Atkinson et al.).

None of the above references teach the use of an HSV vector comprising a nucleotide encoding a human suppressor tRNA molecule according to claim 1 of the instant application.

Okasinski teaches that the HSV (Herpes-simplex virus) vector can be used to produce a helper free viral vector. The invention disclosed by Okasinski an eukaryotic expression vector containing HSV DNA and regulatory elements, and sites for subcloning a DNA of interest. In addition, Okasinski discloses methods of producing a mammalian cell line having cells containing the expression vector.

Therefore, in view of the teachings of the general method of designing and using suppressor tRNAs to by-pass nonsense mutations in proteins in mammalian cells as taught by Sharp et al., the ability of human suppressor tRNAs to suppress nonsense mutations in genes associated with diseases in humans as taught by Tempel et al. and Li et al., the study of codons altered by nonsense mutations and the knowledge given relating to the structure of the tRNA molecule regarding the positioning of regulatory elements taught by Atkinson et al, and finally the advantages associated with the use of HSV vectors taught by Okasinski, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing of the instant application to design oligonucleotides encoding human suppressor tRNA molecules subcloned into HSV vectors in order to produce a cell line expressing said human suppressor tRNA molecules.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-27, and 29-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claims 1-27, and 29-38 recite the limitations "an anticodon region," and "an anticodon sequence," however the scope of the claimed invention is uncertain since it is unclear if the anticodon region is the same as the anticodon sequence, or do they represent separate components of the oligonucleotide sequences of the claimed invention. Additionally, it is unclear if the limitation " a total length of less than 150 nucleotides," refers to the total length of

the oligonucleotide sequences of the claimed invention or does this limitation refer to the total length of the suppressor tRNA.

12. Claims 17-18 recite the limitation "[T]he method of claim 14." However, there is insufficient antecedent basis for this limitation in claim 14. Claim 14 is drawn to a nucleotide vector.

13. Claims 29-31 recite the limitation "[T]he oligonucleotide sequence of claim 28." However, there is insufficient antecedent basis for this limitation because claim 28 has been cancelled.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE